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EDITORIAL

KEEPING UP WITH SCIENCE??

NOT so very long ago, when the last of the alleged ninety-two elements alive was dragged to its seat at the periodic table we breathed a sigh of relief—for here, we thought, was food for a fine and a final tribute to Science's unerring and unremitting results.

This is part of what we were then moved to write, and it was captioned "Standing Room Only—If Any!"

"In July, 1925, we penned an editorial in this JOURNAL, entitled 'The Banquet of the Elements.' The last paragraph read thus:

'So there are now but three empty chairs at the great periodic table. . . .

And the voice of Moseley still persists.

"One by one" it echoes, "until the total comes to ninety-two, not one more, not one less."'

. . . . . .

Today, announcement comes of the discovery of the last of the vagrant three and at the great periodic table every seat has now been taken.

Toastmaster Hydrogen proudly presides at the table head and every guest is in his own belonging place.

To Seat No. 85 belonged the odd distinction of having been the last empty chair—empty—until four American chemists the other day dragged in the last remaining guest and showed it to its proper place with the rest of its elemental kin.

For the first time, then, in all the world's history—man can look upon this assembly of earth's elemental builders, with every member present, 'ninety-two in number, not one more—not one less.'

. . . . . .

The one remaining unknown chemical element, number 85, has been detected for a first time in sea-water, in potassium bromide,

and in a number of well-known minerals by a method of super chemical analysis so delicate that it can recognize one part in a hundred billion of water.

. . . . . .

If the discovery of element 85 is confirmed by other investigators, the United States will have the distinction of having found the three last and therefore the most inaccessible of all the elements and the physical chemist can now draw comfort from the fact that he has at least touched the fringes of a realm which offers still vaster discoveries.

For the atom awaits without—without yet having yielded its power."

. . . . . .

And how little we surmised that before the torrents of a year or so had run beneath the bridge of progress—discoveries had come to pass which vitiate and render futile our picture of a full attendance upon the elemental banquet table.

For one of the most recent—and spectacular scientific finds, has almost made imperative the placing of extra seats at this historic festive board.

According to *Science Service,* Super-uranium, said to be the first of a series of elements heavier than the recognized ninety-two chemical building blocks of universe, has just been discovered.

Scientists are wondering as a result of the report that Dr. Enrico Fermi, brilliant thirty-two-year-old physicist of Rome's Royal University, by atomic bombardment has created artificially a new element, No. 93. He bombarded uranium, heaviest of elements, with the non-electrical particles known as neutrons.

Element No. 93 makes a bid for recognition as the result of this year's fast-moving development in knowledge of the atom's interior which began with the discovery of artificial radioactivity.

Uranium is the heaviest element found in nature, being 238 times as dense as hydrogen, the lightest. For many years it was thought to be the limit of all the possible elements but recently Sir Arthur Eddington and other theoretical scientists have calculated the maximum number of possible elements as 136. Element No. 93 of Dr. Fermi, if its reality is substantiated by competent investigators working independently, may be the first of the super-heavy substances lying beyond uranium in the gamut of chemical elements.

. . . . . .

There was a time when dabblers in chemic theory, searching for the basic constitution of universe, had come to the fanciful conclusion that all matter was built of five elemental things. Four they named—air, earth, fire and water; the fifth, which they knew not, they promptly called the *quintessence,* for lack of a better name.

And, more than likely, they were then quite as certain of the finality of their hypothetical findings as we *should* be today, of anything our scientists tell us. But from now on—we *are not.*

IVOR GRIFFITH.

Phenyl-Mercury Compounds

Phenylmercuric nitrate, $C_6H_5HgNO_3$, is a crystalline substance only slightly soluble (about 1:850) in water. Phenylmercuric chloride, C_6H_5HgCl, is also crystalline and is still less soluble (about 1:20,000) in water. Weed and Ecker emphasize the necessity of careful preparation according to their method, as commercial samples vary greatly in physical characters and bactericidal value; a firm in America makes these products according to Weed and Ecker's specification. The preparations recommended are: (1) a solution of phenylmercuric nitrate, 1:1200, in a mixture of water 90 per cent. and diethyleneglycol 10 per cent. by weight; (2) a solution of the same salt, one part in ninety-nine parts of diethyleneglycol by weight; (3) a solution of the same salt in glycerin, 0.01 per cent. by weight; (4) an ointment containing phenylmercuric nitrate one part in 1500 by weight in an oxycholesterin base; (5) a jelly containing one part of phenylmercuric nitrate in 1500 parts by weight of a mixture of gum tragacanth, glycerin, and water; (6) phenylmercuric chloride, 1:30,000, in 0.85 per cent. solution of sodium chloride.—(Through the *Prescriber.*)

ORIGINAL ARTICLES

THE STANDARDIZATION OF DIGITALIS

By A. John Schwarz*

IN reading the digitalis literature, one is constantly reminded of the variation in digitalis, either in the content of the active glucosides or in its therapeutic activity. Such a condition would naturally lead to the adoption of some method whereby the drug and its preparations could be obtained without a fear of deficient or excessive activity. In response to this, digitalis has been subjected to much study for the purpose of finding a suitable method of standardization. Perhaps no one other drug has had so many methods applied to it as has digitalis. This may be partly accounted for by the confusion that exists among the large number of isolated principles and partly by the failure to ascribe the therapeutic activity to its proper constituent or constituents. That there was need for standardization of this drug is indicated by an expression of Dr. W. Dixon in one of his addresses before a medical meeting when he said (1): "Many hundreds of patients die annually from digitalis and its allies not possessing the virtues which are required of them."

The simplest form of standardization for digitalis finds itself in the proper drying of the freshly collected leaf. As early as 1807, physicians were warned against the use of improperly dried digitalis leaves (2). Tordes (1867) accounted for the superiority of the Strassburg digitalis because the drug in that locality, after careful selection, was dried in the shade and then in an oven not over 40 degrees C.

The first indication of testing digitalis for its activity is recorded in 1846 when M. Falkan (3) suggested making an infusion from 0.5 gram of the leaf, cooling and straining it, and then adding 20 to 30 drops of potassium ferrocyanide solution (0.75 gram in 15 cc. of water). According to this test, the infusion of active digitalis becomes clouded; no clouding occurs within 10 to 15 minutes if the infusion is made from inactive drug.

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The methods of standardization, which have suggested themselves since that time, may be divided into three distinct groups:

1. Those in which digitalis is assayed by chemical methods.
2. Those in which the activity is measured upon animals.
3. Those in which the activity is measured upon plants.

In the presentation of these various methods of standardization that have been used, no attempt will be made at giving the detailed directions of procedure; only the general schemes upon which the assays are based, will be outlined.

Chemical Methods

The chemical methods employed may again be divided into two groups, namely, colorimetric methods and gravimetric methods. No volumetric methods have been devised for digitalis.

Gravimetric Methods:

1. E. Patch's Method: (4) (1891) A gravimetric method based upon R. Palm's method (5) of separation of glucosides by the lead acetate precipitation method and subsequent separation with selective solvents.

2. C. C. Keller's Method: (6) (1897) A determination of the digitoxin content by alcoholic extraction from the leaf, followed by evaporation, dissolving the residue in water, precipitating with lead acetate solution, filtering, making the filtrate alkaline, extracting with chloroform and purifying with petroleum ether. It is then dried and weighed. It was thought that the entire digitalis activity was due to the digitoxin, hence the determination of digitoxin in the assay. In the work of E. D. Reed and C. Vanderkleed (1908) (7) in which Vanderkleed used Keller's method as a check against Reed's physiological method, a direct relationship was noted between digitoxin content and the physiological activity.

3. J. Burmann's Method: (8) (1912) A method very similar to Keller's method, excepting that Burmann used the dialysate preparation and extracted with absolute alcohol.

4. A. Tschirch and F. Wolter Method: (9) (1918) The drug is first extracted with ether to remove the fat and chlorophyl after which the method is that of Keller. Acetone is used as the solvent for the glucosides instead of chloroform, with the result that a mixture of all of the active glucosides is obtained. This assay does not compare favorably with physiological activity.

Colorimetric Methods:

1. W. H. Martindale's Method: (10) (1912) A glacial acetic acid solution of the active principles is mixed with sulphuric ammonium molybdate reagent in a 5 x 1 cm. test tube. The depth of the color developed after 5 minutes is compared with a color scale devised by the author, corresponding to MLD's in physiological standardization. This is an assay for water soluble glucosides.

2. E. Berry's Method: (11) (1919) A variation of Martindale's method in which a value is obtained for total glucosides.

3. A. Knudson and M. Dresbach Method: (12) (1922) A method based on Baljet's color reaction, (13) in which a 1 per cent. alcoholic solution of picric acid and a 10 per cent. aqueous solution of sodium hydroxide are used. The color developed is read against a standard obtained by a similar treatment of ouabain. Conversion tables for expressing this value in cat units have been developed.

Animal Methods

In the use of animals for standardization of digitalis, a large number of assays have been submitted. Not only has the number of assays been large, but the number of species of animals used has also been large. The following members of the animal kingdom have been features in the various assays for determining the value of digitalis leaves and digitalis preparations: Frogs, South African clawed toad, gold fish, guinea pigs, chick embryo, white mice, white rats, paramecia, daphnia, cats, dogs, rabbits, turtles, and pigeons. Of these the frog has been the most popular with the pharmacologist if number of frog methods may be taken as an index. There has been, however, considerable discussion as to the desirability of certain species of *Rana.*

The first report on the use of animals for the observation of the action of digitalis appeared in 1865 and was reported by C. H. Fagge and T. Stevenson (14). A year prior to their publication they began using frogs, injecting them with digitalin subcutaneously and noting the time required to produce cessation of the heart beat. (This method was modified and is now known as the Focke Method.) Robert Koppe (1875) (15) observed the action of digitalis on warm blooded animals, noting the effect upon the heart, but especially the time required to induce vomiting. (This was later suggested by R. Hatcher (16) as a means of standardization.) Koppe noted a

great difference in sensitivity of *Rana esculenta* and *Rana Temporaria,* a factor which is being given some consideration in digitalis standardization at the present time (17). F. Bennefeld (1881) studied the action of digitalis on a rabbit by slow intravenous injection of the diluted preparation into the vein until death occurred. This procedure was later adopted by R. Hatcher in his well-known cat method (18). The guinea pig was suggested as a test animal in digitalis activity by Laborde Duquesnel (1884) in a study of two commercial digitalins (19). The solutions were injected either subcutaneously or intramuscularly. This method is the basis for the Reed-Vanderkleed method of standardization. G. Bardet (1889) (20) used the frog for comparison of activities on the basis of the minimum lethal dose, and is the method adopted by E. M. Houghton in his frog method. J. L. Prevost (1893) (21) used frogs to study the activity of digitalis, choosing the systolic stoppage of the heart as the endpoint.

The first man to insist upon a biological assay for digitalis preparations, and that all preparations be brought to the same strength by dilution or concentration, was Jacquet in 1897 (22). In the following year, E. M. Houghton announced the first method for the biological standardization of digitalis as a result of the work which he had started four years earlier (23).

Frog Methods:

1. E. Houghton 12-hour Frog Method: (1898) (23, 24)—A determination of the minimum lethal dose which is effective in a twelve-hour time interval when a tincture, diluted with normal saline solution, is injected into the ventral lymph sac. Comparison is made with a standard tincture which is being tested simultaneously.

2. Famulener (L. W.) and Lyons (A. B.) 1-hour Frog Method: (1902) (25)—A determination in which the paralyzed heart in systolic stoppage in a time interval of one hour is taken as the endpoint. Forty gram frogs are used and the preparation is injected into the anterior lymph sac through the floor of the mouth.

3. A. Fraenkl 1-hour Frog Method: (1902) (26)—An application of the systolic stoppage method as an exact quantitative assay method for digitalis in which one hour is chosen for the stoppage time, at which time the frogs are pithed and examined. This method was introduced into the U. S. P. IX (1900) for the biological assay

of digitalis, this revision of the pharmacopœia being the first one to require biological standardization of digitalis leaves.

4. H. Ziegenbein 2-hour Frog Method: (1902) (27)—A method in which male frogs are used, the diluted extract being injected into the right thigh lymph sac, and the exposed heart observed. Systolic standstill is expected within two hours. Failure resulted in the administration of larger doses.

5. C. Focke Frog Method: (1903) (28)—A method based upon the amount of 10 per cent. infusion of digitalis which causes the systolic arrest of the heart of a thirty gram frog in 7 to 25 minutes, after injection into the lymph sac. This was the earliest physiological method for digitalis assay generally employed in Germany (29).

6. R. Gottlieb Frog Method: (1908) (30)—A modification of Focke's method in which the time limit is increased to "within 30 to 45 minutes." The unknown preparation is checked against solutions containing definite amounts of known glucosides.

7. J. H. Pratt's Frog Method: (1910) (31)—Essentially Gottlieb's method, excepting that Pratt uses *Rana pipiens* Schreber and Gottlieb uses *Rana temporaria* L. Systolic standstill in this method occurs at the end of thirty minutes.

8. O. Schmiedeberg Frog Method: (1910) (32)—A perfusion method on the heart of a decapitated male *Rana temporaria* L. in which a 1 per cent. infusion is led into the heart, through the aorta, which is connected with a Williams apparatus. The pulmonary vessels and the vena cava are tied off, and the heart suspended in a physiological solution. The heart standstill is taken as the endpoint.

9. Sharp (J. C.) and Lancaster (J.) 3-hour Frog Method: (1911) (33)—Determination of a dose of the tincture that will stop the heart and circulation in three hours after the injection into the dorsal lymph sac of a twenty gram male frog that has been pithed and set aside for 24 hours before the injection. The standard for such a dose is two and a half minims.

10. A. R. Cushney 1-hour Frog Method: (1911) (34)—A method in which the standard dose will produce, at the end of one hour, a white motionless, contracted ventricle and a purple, distended auricle. The frogs are injected in series and compared with a stand-

ard series. The frogs are pithed and the heart exposed sixty minutes after the injection.

11. C. Focke Modified Frog Method: (1913) (35)—A modification made to meet the criticisms of his 1903 method. A determination of the smallest amount of leaf per gram of frog body weight that will cause the typical digitalis heart arrest in thirty minutes or more after the injection has been made into the ventral lymph sac.

12. R. Kobert 24-hour Toxic Frog Method: (1914) (36)—A determination of the minimum amount of tincture to produce death in *Rana esculanta* L. within twenty-four hours after injection into the leg or dorsal lymph sac.

13. E. Berry Heart Perfusion Method: (1915) (37)—A heart perfusion method with cannula inserted in the vena cava, and the two aorta cut as far from the heart as possible and the frog then attached to the recording apparatus where heart beat is recorded on a kymograph, the standstill being the endpoint. The theory is that the amount of drug absorbed is directly proportional to the heart weight and body weight; therefore, the amount absorbed is also proportional to the concentration of the solution and thus to the respective minimum lethal dose.

14. U. S. P. IX 1-hour Frog Method: (1916) (38)—A method based on Fraenkel's assay (No. 3). The diluted preparation is injected into the abdominal lymph sac of the frog, and causes a systolic standstill at the end of one hour. The next smaller dose leaves the heart beating at the end of one hour. This is sometimes referred to as the minimum systolic dose (MSD) method.

15. W. Straub Heart Perfusion Method: (1915) (39)—A perfusion method on the isolated heart of the frog. A cannula is inserted in the aorta opening. Blood is washed out of the heart with saline solution, clamped, the apex connected with cinematograph. The preparation to be tested is introduced through the cannula. The criterion of this assay is to determine the number of cc. to which 1 cc. of the preparation must be diluted in order to show no reaction in forty-five to sixty minutes.

16. Marie Krogh Heart Perfusion Method: (1917) (40)—A modification of Straub's method in which the cannula is inserted into the bulbous of the exposed heart, through the valves and into the

ventricle after which the heart is removed from the frog, suspended in a moist chamber and perfused with Ringer's solution containing the drug. The side of the moist chamber connects with a Marey tambour which records the rate and amplitude of the contractions on a kymograph. Stoppage of the heart is the endpoint. The readings are compared with standard tracings in order to evaluate the strength of the unknown.

17. Pick (E.) Wasicky (R.) Frog Method: (1917) (41)—A method in which a 5 per cent. (25 per cent. alcoholic) extract is injected into the ventral lymph sac of a male *Rana esculanta* L. and the heart exposed after two hours when it should be in systolic standstill. In this method cymarin is used for the standard of comparison instead of ouabain as in some other methods.

18. R. Gottlieb's Frog "Stillstand" Method: (1918) (42)—A method in which the "stillstand" of the frog's ventricle after injection of the active digitalis glucosides and the time required for recovery is taken as an index for evaluating digitalis preparations. The time lapse varies from fifteen minutes to several hours.

19. E. Berry Modified Heart Perfusion Method: (1919) (43)—The 1915 method (No. 13) was modified whereby the preparation was perfused through the whole body instead of the heart only.

20. M. S. Dooley and C. D. Higley Frog Method: (1922) (44)—A method using intramuscular injection into the thigh and then observing the systolic standstill which should occur at the end of one hour. Intramuscular absorption is more effective than lymph sac absorption.

21. Geneva Conference of the League of Nations Method: (1925) (45)—A method which varies from the U. S. P. method by limiting the assay to male frogs and extending the observation period from one hour to four hours.

22. B. Uhlmann Intravenous Frog Method: (1926) (46)—A method in which the lymph sac injection is replaced by injection of the substance into the abdominal vein of the frog in order to avoid resorption error. The standard is a dose sufficient to cause a cessation of heart beat for seven minutes.

23. G. Mansfeld & Z. Horn Frog Heart Sinus Method: (1928) (47)—A method in which evaluation of the preparation is

made by comparing the action of the alcoholic extract with the aid of a microscope on isolated and pulsating material of the frog's heart sinus area. The heart material is immersed in oxygen saturated Ringer's solution. The time requirement is one and one-half hours.

Cat Methods:

1. Hatcher Cat Emetic Method: (1907) (48)—Hatcher observed the emetic action of digitalis and suggested that it might be used as a method of standardization, but the action on the vomiting center was found to be more variable than the action on the heart and so the method was never developed.

2. Hatcher (R. A.) (Brody (J. C.) Method: (1910) (49)—The determination of the amount of digitalis required to cause the death of a kilogram cat within ninety minutes when the drug is slowly and continuously injected into the femoral vein. That amount is known as one cat unit and is equivalent to 0.1 mg. ouabain which is used as the standard. The assay is started with the unknown drug and after a lapse of twenty minutes it is continued with the standard ouabain solution until the cat dies. The value of the unknown solution may then be calculated by difference of the toxic dose of ouabain and the dose actually required to complete killing the cat. Ouabain is capable of replacing any of the digitalis bodies.

3. R. Heinz Cat Method: (1912) (50)—While Heinz's chief work on standardization was concerned with white mice, he also applied the blood pressure method to the cat, obtaining kymograph records after intravenous injection.

4. L. G. Rowntree & D. Macht Cat Method: (1916) (51)—This is not a new method but rather a modification of the Hatcher method, the change being in the time rate of injection.

5. L. W. Rowe Method: (1919) (52)—Like the last-named method, this, too, is a modification of the Hatcher method in which the time required to produce death is cut down to an average of thirty minutes, the limits being twenty and forty-five minutes. The injection is made more rapidly.

6. E. L. Newcomb Method: (1923) (53)—This is another modification of the Hatcher method in which the anesthesia is withdrawn from the cat at the time of injection of the drug so as to avoid chance

of death from the anesthetic which had been noted as a serious objection to the method.

7. A. Magnus Cat Method: (1926) (54)—A 0.5 per cent. infusion is run into the jugular or femoral vein of a 1700 to 2700 gram cat under light ether anesthesia, at the rate of 1 cc. per minute; stoppage of the heart occurs in thirty to fifty-five minutes.

8. W. R. Bond Method: (1927) (55)—This method also follows the Hatcher Brody method, but the minimum lethal dose is based upon the heart weight of the cat, rather than the body weight. This reduces individual variability 30 to 50 per cent.

Dog Methods:

1. Berardi, Canan, McGuigan Dog Heart Rate Method: (1925) (56)—A method intended to measure the therapeutic value rather than the toxic value of digitalis. It consists of an intravenous injection of the extract. The heart rate is counted before and after injection, which count is the index of activity, the count being taken at ten-minute intervals until the greatest drop is recorded. For standard drug, 0.02 cc. of the tincture per kilogram of dog reduces the heart rate 20 per cent. in thirty to sixty minutes.

2. Berardi (J. B.) Dog Method: (1926) (57)—This is an application of the Hatcher method to the normal dog.

Guinea Pig Methods:

1. Reed Vanderkleed Method: (1908) (58)—This method consists of the determination of the lethal dose required to kill a 240-gram guinea pig in one and one-half to two hours after subcutaneous injection of the tincture or fluid extract from which the alcohol has been removed and replaced with water.

2. Knaffl-Lenz Method: (1926) (59)—An application of the Magnus Hatcher Cat Method to 550 to 770-gram guinea pigs that have been starved for five or six hours. The infusion of digitalis is run into the jugular vein at the rate of 0.5 to 0.6 cc. per minute until the heart action becomes weak when the inflow is cut down to 0.1 or 0.2 cc. per minute, the thorax opened and the moment of cardiac standstill noticed.

Rabbit Methods:

1. S. C. Sowton Heart Perfusion Method: (1908) (60)—The isolated heart of a three to four-pound rabbit is perfused with a tincture in Ringer's solution (1:200). The strength of the solution is judged by the length of time necessary to cause stoppage of the right ventricle, shown by kymograph readings. The recording lever is connected to the right ventricle.

2. R. Heinz Rabbit Method: (1912) (61)—While Heinz's chief work on digitalis standardization was concerned with the white mice method, he applied the blood pressure method to the rabbit in the same manner as he did to the cat, obtaining kymograph records after intravenous injection.

3. Nyiri (W.) DuBois (L.) Rabbit Method: (1930) (62)—A method in which the anesthesia is produced by intravenous injection of some barbituric acid derivatives. The infusion of the drug is introduced through the jugular or femoral vein and readings made of the blood pressure. When the pressure is at 0, which occurs a few seconds before standstill, the inflow is stopped.

Pigeon Method:

1. Hanzlik (P.) Shoemaker (H. A.) Pigeon Method: (1926) (63)—This is a method designed for an index of therapeutic potency rather than toxic potency. The digitalis preparation is injected intravenously into the wing vein of a 300-gram pigeon, the standard dose producing vomiting within five to ten minutes. The minimum emetic dose for this method is about the same as Eggleston's dose for man, 30 mg. of digitalis per kg. body weight. The M. E. D. for the standard, which is ouabain, is .045 mg. per kg. of body weight.

White Mice Methods:

1. R. Heinz White Mice Method: (1912) (64)—A determination of the minimum lethal subcutaneous dose followed by an oral administration of like dose to another mouse that has been starved for a few hours. Further similar doses of 1, 2, 4, and 8 times are given orally in food pills at one-hour intervals until death occurs. This is compared with results obtained from g-strophanthin and digitoxin. Death is caused by stoppage of the heart.

2. Marie Krogh White Mice Method: (1926) (65)—Six to ten weeks old mice weighing 18 to 20 grams are injected subcutaneously

with 0.5 cc. of Ringer's solution containing the drug. The injected animals are kept in individual glass cages, and examined every two hours on the first day and twice a day after that. The mice are affected by being less active, unsteadiness of locomotion, inability to walk, and finally death, which in a standard occurs in about three days. Minimum and maximum doses are determined and compared with the results of standards which are carried on simultaneously.

White Rat Method:

1. E. W. Wentz White Rat Method: (1925) (66)—150 to 200-gram non-pregnant rats, starved for twelve hours, are injected intravenously at the rate of 1 cc. per minute, the liquid representing half the strength of the tested tincture. (The toxic alcohol dose is first determined and then the tincture is diluted with saline solution to keep it below the toxic alcohol point.) The toxic digitalis dose of a standard produces death in fifteen minutes.

Gold Fish Method:

1. Pittenger (P.) Vanderkleed (C.) Method: (1915) (67)—A determination of the dilution of the drug in water which will cause the death of *Carrassius auratus* L. in a given time. A 1:1000 dilution of the tincture causes death in about one hour. Weight of the fish is no factor but temperature influences the results markedly.

South African Clawed Toad Method:

1. Gunn (J.) Epstein (D.) Clawed Frog or Toad Method: (1932) (68)—The method employed is the same as the one-hour frog method. These investigators found that the South African Clawed Toad (*Xenopus*) responds more constantly than *Rana* to the digitalis series of drugs.

Turtle Method:

1. W. H. Zeigler Turtle Method: (1916) (69)—A 500-gram fresh water turtle is pithed; the drug is injected into the right aorta—.1 mil of the solution per gram body weight of turtle. The therapeutic effect shows up in three minutes, which is indicated by kymograph tracings. The toxic effect shows up in ten minutes with the heart standstill. The solution used is a 25 per cent. alcoholic extract. Checks are run against a standard.

Chick Heart Method:

1. E. Hall Chick Heart Method: (1932) (70)—Seventy-two to seventy-six-hour incubated eggs are used, the shell membrane is broken and a small amount of the albumen permitted to escape. Microscopic examination of the egg consisted in counting the number of somites and measuring the posterior vitelline vein. (Embryos with 26 to 32 somites and a 9 to 12 mm. diameter vitelline vein are most satisfactory). Ten minims of the tincture are injected into the egg, and the egg then placed in a water bath, observations being made every fifteen minutes until the heart stopped beating. Ten minims of a 1 per cent. infusion of normal digitalis leaf shall stop the standard embryo chick heart in not less than forty-five nor more than seventy-five minutes.

Daphnia Method:

1. A. Viehoefer Daphnia or Water Flea Method: (1928) (71)—This method consists of determining the quantitative effect of digitalis (directly visible under the microscope) and the smallest amount causing permanent inactivity of the organism in a given time unit under controlled conditions.

Paramecia Method:

1. A. Schneider's Paramecial Method: (1925) (72)—*Paramecium caudatum* L. is the organism used in this method. Two cc. of the preparation is evaporated to dryness and redissolved in normal saline solution which constitutes the stock solution from which various dilutions are made to determine the endpoint on paramecia. The standard is a dilution which kills the organisms in three minutes but not in one minute. A dilution of 1:10 does not kill in three minutes.

Finally, in the line of animal standardization, a statement was made by E. L. Newcomb (1923) (73) in a discussion on digitalis standardization that someone had suggested the standardization of the drug on man by means of the electro-cardiograph, the endpoint of the reaction being the measurement of the change in the T-wave.

Plant Methods

The use of plants for drug standardization is comparatively new and not too favorably received. For the standardization of digitalis, only one method is reported.

Macht (D.) Krantz (J.) Plant Seedling Method: (1927) (74)—The digitalis principles are deleterious to the root growth of

Lupinus albus L. Three-day-old seedlings are used, the roots being measured and then placed on top of test tubes containing varying concentrations of digitalis in Shive's nutrient solution. The growth of the seedlings is inversely proportional to the concentration making possible a phytotoxic curve which can be calibrated in terms of cat units.

Because of the well-known variation that exists in digitalis preparations, an international unit was proposed by the Health Committee of the League of Nations which met at Geneva in 1925.(75) It was recommended that a quantity of standardized powdered leaf of *Digitalis purpurea* L. be maintained at Geneva, which is to consist of a mixture of ten different powders made from leaves properly dried at 55 degrees to 60 degrees C. and adjusted by biological assay. The activity of this standard is to be tested annually. The preparation is to be distributed in sealed brown glass ampuls for international use. The methods of standardization recommended by the committee are:

1. The frog method of determining the minimum lethal dose by the so-called unlimited time method.

2. The Magnus-Hatcher-Brody Cat Method.

The international unit is considered as 100 mg. of the standard digitalis powder prepared by the League of Nations.(76)

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CURIOUS REMEDIES—OLD AND NEW

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THERE are people these days who now and then complain that doctors merely experiment upon them. Or they tell about some relative or friend upon whom the doctor tried this, and that, and the other drug, only to have his patient grow progressively worse and incontinently die. But a little contemplation of what medication was two or three centuries ago should convince the most skeptical that "they *aint* heard nothing yet" about the ability of physicians to experiment and to accelerate the hand of Providence in promoting patients to celestial citizenship. Consider, for instance, the death of a gentleman who was able to have as many doctors as he desired . . . in 1685.

Precisely at eight o'clock on Monday morning, the second of February that year, His Most Serene Majesty, Charles II of England, a hearty drinker, a high liver, and a conscientious luster, arose from his bed of slumber. He had a headache. He had been hitting the high spots the night before. For the austere Evelyn records that fact in his famous Diary. He had seen Charles on the previous Sabbath evening, sitting "toying with his concubines," and Charles was deservedly famous for his exquisitely expert toying. A French boy stood nearby singing love songs. Charles sat facing two thousand in gold, well aware that none dare accuse him of criminal hoarding.

Consequently it is not surprising that the King had a headache when he arose the next morning. So he tottered to his closet and took something for it. He took a patent medicine. He took the granddaddy of all the patent medicines, a volatile essence of bones called Goddard's Drops, the discovery of Dr. Jonathan Goddard, a physician then in high repute on the Continent, a man commended by none other than the great Dr. Sydenham himself.

This distillate was carefully prepared from the bones of that part of the body in which the patient was afflicted. Only the leg bone distillate was used to treat rheumatism in the legs, and foot-bone extract for gout. We can imagine King Charles facing a long array of bottles containing every variety of bone distillate he might need, selecting the distillate from bones of the head, and taking some for the relief

of his hangover. Here was born the American bath room cabinet with its impressive array of remedies.

Thus dosed, the King went to be shaved. But in the midst of that tedious operation the King uttered a faint cry and pitched into the arms of Lord Ailsbury who stood or sat nearby. A cry went up for physicians and, fortunately for the immediate comfort of the royal sufferer, only two of them could be apprehended on the premises that early in the morning. But these two were requisitioned and they immediately drew a pound of blood from a royal vein. This was all they could think of at the moment, unassisted as they were, so urgent messengers went forth for reinforcements and very soon two squads of physicians were present and others were on the way.

After a quick consultation the physicians advised cupping glasses to be applied to his Majesty's shoulders and by strenuous efforts and deep scarification they managed to draw another half-pound of blood from the king. Thereupon they administered a strong antimonial emetic, but as the king could swallow so little of it, assurance was made doubly sure by giving him also sulphate of zinc, as well as strong purgatives—laxatives of "sacred tincture," enemas of "sacred" powder—and clysters. Even these measures did not exhaust the physicians' ingenuity.

For they next shaved the king's head close and applied to it pungent blistering agents to drive the disagreeable humours therefrom, and finally resorted to red-hot cautery to add to the suffering monarch's acute discomfort. For since he was first stricken the king had had continual convulsions. Yet he survived the treatment of the physicians with marked fortitude, returned to consciousness, told his own story of his attack, informed them that he had taken Goddard's Drops, and did so well until late Monday evening that his tormentors held a parley of war to concoct more deviltry if possible.

The doctors were still worried about the pressure of those melancholy humours on the king's brain, though they agreed that he was "in pretty good state." In fact they were surprisingly unanimous about almost everything, carefully recording their treatments to the minutest detail, as well as the gratifyingly constant downward trend of their patient's health, signing on the dotted line, one after the other, to indicate that they all agreed that this, or this, or this, was the needed treatment at the moment. So now they administered remedies like powdered white hellebore root to make the king sneeze out his evil humours, and applied noxious plasters to the soles of his feet to

draw the humours thither, while giving him a preparation of cowslip flowers and the spirit of sal ammoniac to strengthen and stimulate his brain.

The king bore this torture with remarkable fortitude and no doubt envied good Charles I whose career was terminated by the fact that in some mysterious way, known only to his executioner, his fourth cervical vertebra was cut through its substance transversely, leaving the surfaces of the divided portion perfectly smooth and even, an appearance which could only have been produced by a heavy blow, inflicted with a very sharp instrument. When the doctors next gathered their brains together they weakened before the king's claim that his throat was sore and gave him aperients and soothing draughts, also something to ward off the scalding properties of his urine by reason of the cantharides they had administered to him.

Indeed the doctors became quite humane and even permitted the king to have broth and light ale without hops. With the therapeutic creativeness so far indicated they ended the labors of the first day and left the king in peace. But early on Tuesday morning another conference was called and this huddle was attended by no less than a round dozen of doctors. The success of their previous treatments persuaded them to continue the same throughout the day, but they again gave the king astringents and a soothing gargle for his lacerated throat. However, they anticipated his convulsions would return, so they began to administer an antispasmodic julep of Black Cherry Water, and other ingredients, then highly esteemed in combatting convulsive disorders. They also took a further ten ounces of blood from their patient but otherwise gave him comparative peace.

Wednesday morning dawned. The king had a relapse, the convulsions returned, and the physicians pounced upon their patient in a body. They now administered the spirit of human skull, a step analogous to the administration of oxygen to a patient of today. This spirit was carefully prepared from the skull of a person who had died a violent death. It was given as a sort of last resort in the hope that it would heal by sympathetic therapy. In their extremity the physicians also used Oriental Bezoar Stone, a concretion found only in the stomach of the East Indian Goat and often spurious. An announcement was issued to the public that the king would "in a few days be freed from his distemper," indicating that the higher harispucy of diplomatic prevarication was well developed even in those days.

On Thursday the king had another attack of convulsions, but his mind remained clear and he now faced certain death with marked calm. Between seven and eight of that day he asked for a priest who arrived and ushered him into Heaven by way of the true Roman Catholic faith. By this act he renounced the quasi-Protestant heresy he had so long half affirmed, whereupon he felt at peace with all men and apologized most sincerely both for not being able to meet God sitting up and for taking an unconscionable time dying. He appeared under some misapprehension to the effect that he was a botheration to the physicians who were, on the contrary, quite evidently enjoying themselves hugely.

On Friday the king was seized with breathlessness. He was again bled and heart tonics were administered. But at eight o'clock his speech began to fail, at ten he was unconscious, and he passed away peacefully just before noon, greatly to the regret of the doctors. His death was attributed to apoplexy, a term most loosely used those days, but no ruptured blood vessel was found in his brain at post mortem. The brain arteries and veins were, however, congested with blood, and various organs contained a superfluity of fluids that they never should have contained at all. The king's constitution was indeed remarkable that after a life of most indefatigable lust he could, at fifty-four, so successfully withstand the determined assaults of more than a dozen physicians for a period of four days.

But he sank lower and lower, the more he was dosed, and finally he passed on. He died, "as peaceable as a lamb," his last words being "Do not let poor Nellie starve," a matter into which we shall refrain from delving here. So much for the reports of the physicians themselves as they were most carefully recorded for posterity. But what does history say? The reply to that query may cast some reflections upon the accuracy of historians. Let us turn to Burnett's *History of His Own Time* and find how King Charles II died, according to a layman's account, writing from hearsay no doubt.

The King had looked better for some time. On Sunday, February 1, he had eaten little all day. That night he went to Lady Portsmouth's, where he "called for a porringer of spoon meat. It was made too strong for his stomach; so he eat little of it." Thereupon the King went back to his royal bed upon which "he had an unquiet night." At last the night was over and we read that—

"In the morning came one Dr. King, a physician, and a chemist came, as he had been ordered, to wait on him. All the King's dis-

course was so broken that he could not understand what he meant. . . . He was scarce come in, when the King, who seemed all the while to be in great confusion, fell down all of a sudden in a fit like an apoplexy; he looked black and his eyes turned in his head." The confusion in our own case is undoubtedly caused by a certain vagueness in the objects of the pronoun "he," but we may as well persevere at this thing, once we have started, and get the gossip's accounts of the King's illness.

"The physician (obviously Dr. King), who had been formerly an eminent surgeon, said it was impossible to save the King's life, if one minute was lost; he would rather venture on the rigour of the law, than leave the King to perish. And so he let him blood," the act that started Charles upon his precipitation into the grave. "The King came out of that fit; and the physicians approved of what Dr. King had done; upon which the Privy Council ordered him a thousand pounds, which was never paid him." We pause here to reflect upon the unpaid bills of doctors throughout the centuries of men.

But "tho' the King came out of that fit, yet the effects of it hung still about him, so that he was much oppressed. On Thursday a second fit returned." Then we are told of the sending for the priest, and of how "The Hostic stuck in his throat (the King's, not the priest's, apparently); and that was the occasion of calling for a glass of water. . . . The King suffered much inwardly, and said he was burnt up within; of which he complained often, but with great decency." Here is no picture of a feverish gentleman thrashing profanely about his bed of illness, delivering himself ever so often of great oaths. Instead we have the doctor's and the trained nurse's ideal patient who complains some, but always in a refined manner.

From this point we leap rather unexpectedly to the post mortem and we learn something that is chastening about the grandeur of dead monarchs. For thereafter "The King's body was indecently neglected. Some parts of his inwards, and some pieces of the fat were left in the water in which they were washed; all which were so carelessly looked after, that the water being poured out at a scullery hole that went to a drain, in the mouth of which a grate lay, these were seen lying on the grate many days after. His funeral was very mean. . . . So many of the small veins of the brain were burst, that the brain was in great disorder, and no judgment could be made concerning it."

. . . The King had had his day. It is recorded that as a mere boy he wrote to his tutor, the Duke of Newcastle, advising him not to take too much physic—"for it doth alwaies make me worse, and I think it will do the like with you." We may not admire the King's orthography, but his therapeutic skepticism has its moments. Later in life, when attending the Newmarket races, Charles II amused himself by conferring the degree of medical doctor quite indiscriminately, the holders of these bogus titles being called "jockey doctors."

The man was not respectful to the medical profession. He justly deserved punishment. So ultimately the Lord, in his justice and mercy, gave the doctors their most sweet revenge. Fourteen of them closed in upon the prostrate King and devised discomforts to render his final hours agonizing. In the end His Most Serene Majesty took the only possible means of ridding himself of their abominable ministrations and launched out into the Great Unknown crying: "Do not let poor Nellie starve!" Whether Nellie starved or not, it does seem only just to observe that doctors have improved a very great deal since 1685. So much for the efforts made to cure King Charles II of a headache.

The orthodox remedies of earlier days were many and curious. In mediaeval times human skin and the fat of dead men were in demand for therapeutic purposes. Belts of human skin were most efficacious in easing labor pains, while straps of human skin were listed in the Danish Pharmacopœia for 1672. Human fat appeared in the same book in 1619, 1645, and 1672, and was recommended for external application to strained sinews and ligaments and wasted limbs.

The apothecaries of Paris and certain other cities often complained about the unethical sale of human fat directly by executioners, because this deprived the middle man of his profit. They said: "We sell human fat, obtained from various sources, flavored with savory herbs, and incomparably better than that retailed by the hangmen." Doubtless hangman's fat from sundry criminals was somewhat inferior in healing powers to human fat obtained more mysteriously from "various sources." In Norway both hangman's fat and human fingers were sold, the latter being used to add spice to ale.

Mummies also were much used 300 years ago for medicinal purposes. The difficulty was falsification and adulteration, if not actual misbranding and deceptive advertising. A Tugwell Bill was indicated, for many of the so-called mummies were said to have been actually the bodies of recently deceased citizens. Others came from

Africa and were nothing more nor less than the bodies of those who had drowned at sea that were withdrawn by unscrupulous persons, dried in the sand, and sold as genuine white mummies.

When the ancient physician prescribed mummy for a bad headache his patient rather infrequently got the genuine article. One expert of the day wrote: "I shall only advise such as buy to choose what is of fine shining black, not full of bones and dirt, of a good smell, and which being burnt does not stink of pitch. Such is reckoned proper for contusions, to hinder blood from coagulating in the body. It is also given in epileptics, vertigoes, and palsies. The dose is two drachms in powder, or the same made into a bolus. It also stops mortification, heals wounds, and is an ingredient in many compositions."

There were then five distinct kinds of mummies—the factitious, the modern, the true Egyptian, the true Arabian, and the Artificial. To prepare artificial mummies the pharmacist was supplied with the following receipt:

"Take the carcass of a young man (some say red-haired), not dying of a disease, but killed, let it lie twenty-four hours in clear water in the air, cut the flesh in pieces, to which add powder of myrrh and a little aloes, imbibe it twenty-four hours in spirit of wine and turpentine, take it out and hang it up for twelve hours, then imbibe it again, twenty-four hours in fresh spirit, then hang up the pieces in dry air and a shady place."

This preparation offered a cheerful and a stimulating afternoon's work to the apothecary for several days running, and you may picture in your mind's eye the jaunty effect of his back yard with strips of human mummy hung up on all the clothes lines to dry. To say that pharmacists do not have it easier today would be to deny obvious facts. These esoteric processes of the apothecary who had to procure his man, not dead of disease, but killed, doubtless accounted for many a mysterious disappearance in those simple days when medicine was medicine and the sick were glad to get it.

Made into a balsam this mummy material had such a piercing quality that it rapidly penetrated to all parts of the body, restored wasted limbs, cured consumptions, and remedied corruptions and ulcers. Human fat was also much esteemed for rubbing on in rheumatism. Human skull, preferably grown with moss, probably of fungoid origin, was also valuable medicine, special virtue inhering in skulls taken from gibbets which were administered in powdered form. Many a man was an internal bonehead in those days. Then it was

that human hair cured jaundice, finger nails were used as an emetic (detached from the hands it is understood), hot blood drawn from a healthy man cured fits, duck liver was helpful in kidney disease, and brain was rubbed on the gums of infants to aid them when teething.

Many such notions have survived into modern times. Read the "Catalogue of Morbific Products, Nosodes, and other Remedies in High Potencies," issued by Samuel Swan, M. D., in 1886, and listing the medicaments he found especially efficacious and sold to others. Dr. Swan held that "there can be no standard for measuring the degree of dynamic potency of a medicine, except the degree of reaction of the vital force against it." He offered his remedies by mail in any potency desired and usually a drop of them distributed throughout a lake the size of Huron would make strong medicine.

The seeds of diseases were everywhere at all times, Dr. Swan held. "Morbific matter will cure the disease which produced it, if given in high potency." A disease should be cured a symptom at a time. Say a disease has five symptoms and you give a medicine which clears up two of these; you have three left. If these remain strongly a new medicine is indicated, because a repetition of the same drug might easily bring back the two symptoms already cured. In other words the symptoms get confused, forget they have been cured, and return to plague their victim. Among the remedies that Dr. Swan offered for sale were the following:

Lice; renal albumen from urine; worm bark for blindness, because the smoke of this wood blinds persons; celery; water for sea sickness caused either by riding on water or on cars; spiders to prevent or cure carbuncles; cockroaches; Buffalo Lithia water; Columbian seagull for "uncontrollable desire for coitus"; gravel from the lungs; biliary calculi for gall stones; tobacco ashes to cause relaxation of the anal sphincter; dropsy serum; eel skin; yellow, blue, or red ray of spectrum; Brazilian crickets, because "A boy who had chills and fever swallowed a live cricket and never had a chill afterward"—which might be explained in many ways; roasted snails for hemorrhage of the lungs or internal organs and consumption; "tears of a young girl in great grief and suffering for melancholia"; diabetic sugar from urine; the wood of a tree which was said to cause gonorrhea in those who work upon it; lining of eggs for displaced uterus; lice from the genital region; a crystalline, fatty substance containing phosphorus but made from the brain of a dark complexioned man, aged 45, who had Bright's disease"; material "from a silk handker-

chief eaten by a cow, and taken from the stomach in a hard ball. During the three years she never had a calf"; "menstrual blood from a woman who had warts, and with which many have been cured"; "blood from a yellow fever patient while moribund."

Another remedy not in Dr. Swan's arsenal, but which he apparently recommended, was the so-called "*Sal celebri*—Salt secreted profusely from a gentleman's scalp, with the perspiration, and on drying, it was crystallized so heavily, his head looked frosted."

In more recent times the mind of man has produced even more extraordinary remedies. It has devised methods of selling pure Glauber's salts, worth 39¢ a pound or so, at $1.50 a pound, as a remedy for the diseases of middle age, and Epsom salts, worth 6¢ a pound, at 85¢ a pound, as a remedy for obesity. It has produced in a common horse liniment an effective remedy for tuberculosis of the lungs, a penetrating germicide which bores directly into the tissues, locates the tubercle bacillus wherever he is, grabs him rudely by the scruff of the neck, and casts him out through a skin pore before he knows what has happened to him. It has presented us with an extract from the common weed jocularly known as horsetail which, being a fairly powerful diuretic, convinces many diabetics that they have reduced their urine sugar miraculously after imbibing it at $12 a pint. It has produced an ordinary berry and fruit jam and sold it successfully to the public as a rejuvenating agent; it has placed senna in attractive packages and has sold it as a mysterious herb tea of Germanic origin to aid in reducing the corpulent; it has impregnated a cold cream with the deadly rat poison, thallium acetate, and advised women to use it freely as a cold cream for depilatory purposes, and it has fabricated extraordinary gadgets and machines without number, priced them exorbitantly, and induced those with Durante noses, Maewestian mammary glands, ears that make them look like taxis with both doors open, large clutches of adenoids, or deficient height, to use them and recommend them to others.

There are also persons in this country, living in our so-called modern age, who persist in believing in the verity of therapeutic principles that are essentially magical in character. It will be less invidious, perhaps, if we observe such beliefs at a distance, rather than as held by certain cultists in our very modern midst—which might prove humiliating.

China has an ancient and an honorable system of medicine. It is based on the idea that cosmos arose out of the cooperation of the

yang or male and the yin or female principles. Health therefore depends upon the harmony and equilibrium of these principles—on an even balance between weakness and strength, between heat and cold, between moisture and dryness. It is also true of some very notable modernists in medicine today that they think health is a state of equilibrium. They do not regard any specific factor as the cause of a disease or any other specific factor as its cure, but hold that health is an equilibrium of many factors and illness the reverse.

The Chinese, however, held that of man's 12 organs 6 were governed or dominated by each of the principles noted; when yang predominated there was excitement, but yin brought depression—the female principle, please observe. Man's 5 main organs corresponded to the 5 elements, the 5 stars, the 5 colors, and the 5 sensations, thus—Stomach, Saturn, Earth, Yellow and Sweet; Liver, Jupiter, Wood, Green and Sour; Heart, Mars, Fire, Red, and Bitter; Lungs, Venus, Metal, White and Sharp or Biting; Kidneys, Mercury, Water, Black and Salt.

Man's chief organ was the heart which, with the aid of his stomach, originated thought, though the stomach was also the organ of respiration, the lungs being used to expel humours, the gall bladder to purify the body of fluids and being the seat of courage. The liver was the seat of sensations. The brain and the spinal marrow secreted semen. The right kidney was the seat of the sexual functions. The pulse indicated bodily disturbances, but it also varied with age, sex, the emotions, the season of the year, the hour of the day, and it occurred in 57 different varieties. It therefore took 2 years to master the technic of Chinese pulse feeling alone.

Most of the remedies came from plants, but in consumption a gelatin made from asses' skin and orange peel compounded with salt, vinegar, and urine were used. Diseases of the kidneys were treated with pig kidney. Hemorrhoids, which Napoleon had, and which he wrote his brother Jerome he cured by leeches, the Chinese cured with a very simple remedy containing gentian, aconite, ginger, nelumbo, gypsum, borax, powdered rhinoceros horn, burnt hair, and garlic. Powdered dragon's bones cured nose bleed, but this drug was very frequently adulterated for reasons that may occur to the careful thinker.

Nevertheless the Chinese were vaccinating with scabs for smallpox in the tenth century and they held that this infection was spread from pustules by the wind. Malaria was treated with magnolia,

boiled tortoise heads, buffalo cheese, and iron oxide. Syphilis had been treated with mercury since the tenth century, calomel or the sublimate being used. Diphtheria was treated by blowing an astringent powder down the patient's throat, while licorice and rhubarb were common remedies. Cubebs were used for gonorrhea and asparagus as a diuretic. The penis of deer, asses, seals and sheep, as well as human placenta, compounds of licorice and human feces, deer wombs, tiger bones, oven soot, fossil ivory, the spleens and livers of executed criminals, and many insects were all used in Chinese medicine. One remedy was called Thunder Pills. Others were—opium-weaning grease, sure remedy, robust-the-whole-year.

It should be stated in justice to the Chinese doctors that only about a hundred years ago a French physician advised a mixture of the white part of chicken dung with wine as an excellent bladder remedy. It seems that the Arab pharmacists of the Middle Ages deserve a word. They were polypharmacists par excellence and argued that a remedy must contain a base, the elements necessary for that base, elements which added to the action of the base, and elements which when mixed were later to be replaced by others. It is written of one of them that:

"Opium is the base of this electuary; but you will find here other drugs to augment the action, and as these drugs are of bad quality, others are added to correct the fault. Yet this is not all. They heap up an enormous quantity of drugs, which are charged with such virtues as direct the action of some parts of the medicine to the head, others to the lungs, others to the heart, the stomach, the spleen, the kidneys, and other parts of the body. Thus the refreshing and narcotic property of opium is increased by the addition of henbane and mandragora bark, while the undesirable qualities of the latter are corrected by myrrh, euphorbia, and castor oil. Their action is directed to the head by means of cloves, of peony and sage, of aloes and incense; they penetrate the lungs through the action of sulphur, thyme, and adroganli; finally, they are directed to the heart by the addition of pearls, *blatta odoratus,* gold, silver, stag's bones, and ivory. They are directed to the stomach by mastic"—and probably to the City Hall by the nearest traffic cop.

The Arabian pharmacist had many methods at his disposition. If he thought his drugs were bad or were unsuited for the purpose in hand, he could use them anyway and add other drugs to counteract their bad effects. Moreover he could direct the effect of any one drug

to any part of the human body he wished by putting it in police custody of some other drug. These were the days when a remedy or prescription often contained 40 or 50 ingredients and when, from time to time, the pharmacist became determined to effect a cure and dumped in every drug in the pharmacopeia.

Ancient medicine and pharmacy were not all bad, however. The juice of citrus fruits had been used for the treatment of scurvy in Florence during the Middle Ages. Cod liver oil was used to cure rickets early in the last century, but its efficacy somehow became forgotten. Licorice, as we have seen, was used by the apothecaries of ancient China. Hippocrates also advised it as an external application for sores with honey or in an ointment, and Nero's personal physician used it in his celebrated theriaka. The Hindus used licorice for thousands of years as a tonic, and the Norwegians as a counterpoison. It is now used to some extent as a remedy for acid stomach and intestinal inflammation.

For thousands of years the Chinese also prescribed the heads of powdered toad fish as a remedy for heart trouble. These have now been discovered to contain adrenalin. The American Indian habitually preferred the liver of animals killed; he was called ignorant, but modern nutrition science indicates that he knew what he was about.

The history of the Chinese toad is very interesting. Its dried venom was long in the Chinese materia medica. As early as 1596 it was recommended for external application to canker sores, in sinusitis, for toothache, gum hemorrhages, inflammatory conditions, and also for administration internally as part of a compound pill that was the one-night cold cure of its day. Powdered toad was recommended for dropsy and other ailments in a book published in Holland in 1672. It was found in 1929 to contain epinephrin or adrenalin.

As Crookshank once wrote: "Much more of which we boast ourselves is but a restatement in other languages—sometimes less truthful than before—of futile explanations which are acceptable because familiar by analogy. So, a dose of castor oil acts with equal efficiency whether given to expel a demon, to calm the vital spirits, to assuage the Archaeus, to evacuate morbific humours, to eliminate toxins, to restore endocrine balance, or to reduce the blood pressure."

Something was said earlier of the ridiculous side of high potential homeopathy and more could be said if we had room on any ordinary sheet of paper to set down the mathematical calculations involved in determining a truly high potency. But there is much more

than a touch of homeopathy in many modern remedies. Hahnemann is said to have taught that very minute and easily licked doses of nitroglycerine would increase headache resistance. There is a type of headache peculiarly associated with high blood pressure, and there are times when minute doses of nitroglycerine will stop such headaches by bringing the blood pressure temporarily to normal. But nitroglycerine did not prove to be a symptom-specific vaccine because repeated doses of it produced no immunity to any kind of headache.

But in such a thing as immunization to cobra snake venom we have a resemblance to homeopathic theories. Normal laboratory animals usually die of cardiac paralysis when injected with moderate doses of the venom. An excised animal heart, kept alive under artificial circulation, usually dies or ceases to beat in from five to ten minutes after a milligram of cobra venom is added to the circulating fluid. But immunization can occur by the administration of subtoxic doses of the venom though the immunity is highly specific for this one morbidic agent and offers no protection against other zoo-toxins, much less other types of poison. Again our modern usage of exceedingly minute doses of certain glandular products, such as adrenalin, in a way smacks of the homeopathic high potential remedies.

We have, however, discarded many unique and powerful medicines. Robert Boyle, the great philosopher-chemist, for instance, recommended a mixture of rubies, sapphires and horse dung taken internally, with powdered wood lice for a chaser. He could also prepare a powerful extract from certain herbs which would cause an old hen to moult immediately after she drank it, though a few days thereafter she grew new feathers and acted in all points as if much rejuvenated by her experience. Boyle recommended castile soap for jaundice, ashes of pig dung for dysentery, and powdered earth worms for convulsions, not to mention powdered hare's liver for epilepsy.

Most interesting and economical of all, perhaps, was Nicolas Lemery's famous cathartic pill, or perpetual purge, which he described as follows: "If you melt antimony over again and form it into bullets of the bigness of a pill, you have a perpetual pill, that is to say, such as being taken and voided fifty times will purge every time and yet there is hardly any sensible diminution." It might be well to say that Lemery was French, not Scottish.

Something should be said about the Japanese patent medicine business which was founded by a Prince born in 1649, who was ruler of his province and who distributed very efficacious medicines

for dysentery. Somewhat later one Bandai Jokan, a physician of another province, discovered a very fine remedy which he called Han-Gon-Tan or the medicine-which-calls-the-dead-back-to-life—one might say the Undertaker's Surprise. About 1690 the Prince used this with marked effect upon another member of the nobility taken ill at the Shogun's court; thereafter he went into the patent medicine business on a large scale. He caused various medicines to be distributed from door to door by peddlers. They were left without payment but the following year when the seller returned the buyer paid for the medicine used, got a rebate on the unused portion, and took another consignment.

The business expanded rapidly and by 1904 there were nearly ten thousand different kinds of patent medicine sold in Japan. They were recommended to guard against illness, to exhilarate the spirits, to clear the voice, to increase physical or mental energy, to change the color or constitution of the skin or hair, to remove unpleasant smells—B. O. or halitosis, and to heal skin diseases. None of the medicines were in liquid form, all being pastes, pills, powders, or ointments. Some of the names of the more popular were, in English: Brain-healing pills, spirit-cheering pills, heal-everything powders, touch-the-spot pills, real-mother-medicine for female complaints, twice-eight-water to make any woman look 16, and pick-me-up-pills to make any man, no matter how old and feeble, act that way when he saw a woman of 16.

It is superfluous, in conclusion, to dwell upon modern times when we have at last evolved thoroughly rational and scientific remedies and never under any circumstances deviate into magical or unscientific medication. Perhaps one example will suffice. This is, as it should be, The Spectro-Chrome, which is the name of a machine and also of a periodical, of which the March, 1934, issue is in hand as these lines are written. The trade-mark is registered in the United States Patent Office and the organization conforms to N. R. A. requirements. This is Volume 10, Number 3, and March, in case you are interested, is decidedly yellow. The masthead of the magazine states—

"Spectro-Chrome, A Monthly Magazine Devoted to the Service of Mankind—Publisher and Editor Dinshah P. Ghadiali—Official Publication of the Scientific Order of Spectro-Chrome Metrists—(A Not-For-Profit Corporation of the State of New Jersey)." An announcement to the public follows in which we read: "We accept no

gifts or gratuities, as to a Public Servant, it is Graft. Send us nothing." On page 1089, it still being Yellow 1934, we learn that the Spectro-Chrome Institute is fighting for its life against the Tugwell-Copeland Bill, which is also fought by another non-profit organization in New Jersey at Washington. There follows a letter of protest to Senator Copeland which was written Thursday, January 25, 1934, Chronos, Green 45 Black, to which the Senator replied that he was interested to learn his correspondent's point of view. He next received a letter dated Thursday, February 1, 1934, Chronos Turquoise 05 Black, in which he was wished the best of health and several other things, though not a Merry Christmas, and to which he did not reply apparently.

However, on page 1094 of this March-Yellow 1934 Spectro-Chrome we learn that the Senator lost his pants, the Senator being quoted to this effect in his report on the Suppression of Crime, a fact that seems vaguely irrelevant, but no more so perhaps than everything else in the publication. There follows a letter of expostulation to one Mr. Rexford G. Tugwell, written also Thursday, January 25, 1934, Chronos, Green 30 Black, to which no reply appears. Then Mr. Ghadiali took his typewriter in hand and January 25, 1934, Chronos, Green 55 Black, possibly somewhat later in the day, telegraphed Senator Stephens registering emphatic protest against the Tugwell-Copeland Bill. Finally, on page 1097, we find a letter addressed to the President of the United States, also written January 25, 1934, but the Chronos was then Green 15 Black and it is impossible to tell whether it was getting any later or not. However, the President was celebrating his birthday and did not reply.

By this time you will want to know what Spectro-Chrome is. It is a healing system. It heals anything. It is a device. On page 1103 of this same magazine we come upon "Favoroscope for Spectro-Chrome Metry Dinshah Sympathometer System March 1934 Yellow, Chronos or Time Table, set to standard time for home use." There follows on the next page the "March correction formula for locality," and if you live in Trenton, N. J., you subtract 1 in the day and 1 in the night, but in Philadelphia you must add 1 both times, while in Vineland, N. J., or Malaga, N. J., you are smack on the Spectro-Chrome Meridian and there isn't a thing you can do about it. On page 1108 we come to April, 1934, which, by the way, is lemon.

Does the system work, you ask? Does it work? See page 1111 and read about "Sinus Trouble, Weak Heart Normalated, an Unsolicited Expression" from Milwaukee. One "tonation" last November and the gentlemen never had the slightest recurrence. Or consider the reports from the "First Detroit Michigan Planet, Minutes of the Regular Meeting of February 1, 1934," on page 1115. One or two of the cases deserve quotation—

"Otto Hinz, a new member in our planet, gave quite a detailed report of his experiences with Spectro-Chrome. His condition being known as Asthma, Lemon Systematic and Orange Systematic and Magenta on Areas 418, were the Attuned Color Waves used to normalate his condition." Otto really preferred vanilla or pistachio, but the fountain clerk said there was a limit to his ingenuity. Quoting again, now from the "First Milwaukee-Wisconsin Planet"—

"Lillian Goebel is tonating a School Teacher who had pains for 15 years and after 12 tonations she says it is the first time in 15 years she has had no pain. The Attuned Color Waves started with Green, Lemon, Yellow and now Orange. . . . Otto H. Lutz has a case of a man who claimed he had a dropped stomach (it is not said who dropped it on him), sinus trouble, severe pain in the back, and a tendency to forge checks. His disorder is of long standing. As he refused to sit down Orange and Lemon Systematic were given; also Orange and Red given for Local and Magenta on Areas 4 and 18. So far he has had five weeks of Spectro-Chrome and is feeling well."

One lady with a fulminating appendix was tonated till "The Kardoscil now is 74, Spiroscil 16; Lemon Front Systematic and Scarlet on Area 4 are the Attuned Color Waves used." We need say nothing further. It is very obvious that we have reached a point in scientific development where our people no longer believe or have any use at all for magical or pseudo-scientific methods of treatment. Scientific pharmacy has come into its own at last and we close with the happy poem which also closed the issue of the Spectro-Chrome just quoted—

> O happy Release! O felicitous Freedom!
> Liberty, the greatest of human birthrights!
> What words, implied or expressed, can mean
> The depth of what my harassed soul feels?
> O wondrous Release! Release from strain,
> From incarceration, unjust imprisonment,
> Of my body by operation of grafty laws,
> No one can portray the quiver in my heart.

SCIENTIFIC AND TECHNICAL ABSTRACTS

Compiled by Arthur Osol, Ph. D.

Volumetric Determination of Iodides. R. Uzel. *Collection of Czechoslovak Chemical Communications, 5,* 383 (1933) through *Pharm. Zentralhalle 75,* 243 (1934) #15. The volumetric determination of iodides as silver iodide in the presence of cinchonine-bismuth nitrate indicator has been developed and is recommended as a clear-cut and accurate method. When all of the iodide has been precipitated the red color of the indicator disappears. The indicator is prepared by dissolving 2.33 grams of bismuth oxide in 10 cc. of concentrated nitric acid, to which is added 2.94 grams of cinchonine and the mixture diluted to 100 cc. Ten to twenty drops of this mixture are used in the titration. The end-point is sharp and chlorides and bromides interfere only if they are present in considerable excess.

Are the Alkali Bromides Therapeutically Equivalent? von W. Ripperger. *Therap. d. Gegenw. 74,* 348 (1933) through *Pharm. Zentralhalle 75,* 260 (1934) #16. It is reported that an epileptic who had taken a mixture of 90 per cent. KBr and 10 per cent. NaBr for a year (with good results) and then changed, without the patient's knowledge, to a mixture of the reverse composition did not find the latter effective and was subject to frequent attacks. Improvement was noted upon returning to the original combination. If the effect of the medication were dependent solely upon bromide ions, as has been assumed for a long time, the action of the mixture of 90 per cent. NaBr and 10 per cent. KBr would be more pronounced since NaBr contains 77 per cent. bromine compared to 66 per cent. in the case of KBr. Other effects must therefore be taken into consideration.

Detection of Sucrose in Lactose. M. Wagenaar. *Pharm. Weekblad. 71,* 281 (1934). Through *Chem. Abstracts 28,* 3030 (1934) #10. The method is based on the fact that ketoses (fructose) give a violet color with alpha naphthol and sulphuric acid while aldoses remain colorless. A five milligram sample of the lactose is suspended in a drop of a glycerol solution of alpha naphthol, and a drop of concentrated sulphuric acid stirred in with a platinum wire. If sucrose is present, a blue-violet color develops within ten

minutes. The reaction may be rendered more sensitive by warming the mixture for half a minute on a water bath and comparing the color with that of a control test with pure lactose. One per cent. of sucrose can readily be detected.

Ultraviolet Irradiation of Milk. Science News Letter, May 26, 1934. Milk that has been irradiated by exposure to ultraviolet light keeps longer, has a slightly lower bacterial count and lower acidity than has ordinary whole milk. This added keeping quality of irradiated milk has been proved through research work done during the past year by K. G. Weckel and H. C. Jackson of the University of Wisconsin. They found that at refrigerator temperatures irradiated milk will keep several hours longer than whole milk not so treated. This added keeping quality is partly due, the experiments show, to a very slight reduction in the development of acidity of the milk after irradiation.

Irradiation also causes a slight reduction in the bacterial count in milk, but the process has no specific effect on some of the most important milk bacteria, namely the lactic acid, gas-forming and coagulating types. This seeming contradiction is explained by the fact that the exposure of the milk to the ultraviolet light is for such a short period, and that the opaqueness of the milk furnishes a protective film against the light rays.

In high quality milk of low bacterial count the percentage of bacterial reduction by irradiation was found to be very low. But in poorer quality milk, high in bacteria, the reduction was somewhat higher. In neither case was the bacterial reduction great enough to indicate that the reduced acidity in irradiated milk was caused by the smaller number of bacteria. Many large and small milk plants have during the past year installed machinery to produce irradiated whole milk.

Assay of Alkali Salicylates and Benzoates. American Drug Manufacturers Association Recommendation. Twenty-third Annual Meeting, April 16-19, 1934. That a satisfactory assay for the alkali salts of these organic acids has been desired is evident from literature references extending over the past three decades.

The U. S. P. method which depends upon ignition of the salts and titration of the residue as carbonate is accurate when carefully performed, but is rather long.

In the Journal of the A. Ph. A., vol. 22, page 954, Schmidt and Krantz offer a simplified method as follows: "Transfer about 1.5 gm. of salt, previously dried to a constant weight at 100 degrees C. and accurately weighed, to a tall beaker of about 300 cc. capacity and add 75 cc. of ether and five drops of methyl orange T. S. Titrate the mixture with half-normal hydrochloric acid, mixing intimately the aqueous and ethereal layers by vigorous stirring, until a permanent orange color is produced in the aqueous layer."

This method follows closely the assay used in the B. P. 1932. Less water and more ether is used than in the B. P. method. These are improvements. The method, however, differs markedly from the B. P. directions by omitting the replacement of the ether layer with fresh ether, just before the end-point is reached. In the case of sodium benzoate this introduces but slight error. However for sodium salicylate this procedure gives low results.

This was verified by comparative assays on various samples and indicated results which were about 0.8 per cent. low. If the aqueous layer at the end-point is removed and treated with fresh ether the true end-point is obtained. It is recommended that the following addition be made to the proposed method: "Transfer the contents of the titrating vessel to a small separatory funnel and run the aqueous layer into a small clean and dry flask. Wash the ether layer once with 5 cc. of water and add to the separated aqueous layer. Add 20 cc. fresh ether and continue the titration to an orange color which persists on vigorous mixing of the two layers. Each cc. of half normal hydrochloric acid corresponds to 0.08004 gm. of C_6H_4.OH.COONa. (The Drug and Cosmetic Industry *34*, 475, 1934.)

International Method of Assay of Opium. L. van Itallie. *Pharm. Weekblad. 71,* 4 (1934). Through *Quart. Journ. Pharm. Pharmacol. 7,* 122 (1934). An investigation of the methods of assay of opium has been carried out by a Committee of the League of Nations. It appeared that only a lime method could be recommended for general adoption, and the one finally recommended is one based on that of the British Pharmacopoeia, and now adopted in the new Swedish and Danish Pharmacopoeias. Although the method makes use of a correction for dissolved morphine, and it is recognized that this amount is not constant, it is considered that the results approximate closely to the true values. The method is as

follows: Four grams of the opium is rubbed down with 1 gram of calcium hydroxide and 10 mils of water. An additional 10 mil portion of water is added, and the mixture is stirred at intervals during a quarter of an hour. It is then transferred to a tared flask, made up to 45 grams with water, and shaken well for half an hour. The mixture is then filtered on a sintered glass filter (3G3) with a slight vacuum. Three grams of the filtrate is evaporated and dried at 103 to 105 degrees C. to constant weight. The extract content per 100 grams of opium is then

$$\frac{(100 + F)M}{3 - M}$$

where F is the moisture content (103 to 105 degrees C.) of the opium, and M the weight of residue from 3 grams of filtrate. Another portion of 25 grams of the filtrate is mixed with 2.5 mils of alcohol (90 per cent.) and 12.5 mils of ether, and shaken. One gram of ammonium chloride is added, and the mixture is shaken vigorously for five minutes and at intervals during half an hour. It is allowed to stand overnight, well shaken, and filtered on a 3G4 sintered glass filter under slight vacuum, the liquid not being allowed to rise to the top of the filter. The residue is washed with 3 mils of ether, then with 3 mil portions of a saturated solution of morphine in water until the filtrate gives no further reaction for chlorides. The flask in which the morphine has been precipitated, and the filter, are dried for thirty minutes at 103 to 105 degrees C. After cooling, the rim of the filter is smeared with soft paraffin. The small amount of morphine in the flask is dissolved by warming with 10 mils of methyl alcohol, which is then poured through the filter, and this is repeated with another 10 mil portion. The filtrate is cleared, if necessary, by warming, and titrated with N/10 acid, using methyl red as indicator, to a faint orange color. After the addition of 120 mils of boiled water the titration is continued until the color begins to change to red. The morphine percentage of the anhydrous opium is then equal to

$$\frac{(1000 + E + F)\ (A + 1)\ 0.114}{100 - F}$$

or on the original opium

$$\frac{(1000 + E + F)\ (A + 1)\ 0.114}{100}$$

where E is the percentage of extractive calculated as above, and A the number of mils of N/10 acid used in the titration. In this formula a correction of 1 mil of N/10 acid, or 28.5 mgm. of morphine, is allowed for that remaining in solution.

Decomposition of Solutions of Soluble Phenobarbitone. L. Nielsen. *Dansk. Tidss. Farm. 7,* 137 (1933). Through *Quart. Journ. Pharm. Pharmacol. 7,* 130 (1934). In aqueous solution, sodium phenylethylbarbiturate slowly hydrolyzes with formation of phenylethylacetylcarbamide and carbon dioxide. The amount of carbon dioxide present in such a solution may be determined by precipitation with barium chloride; while the phenylethylacetylcarbamide may be determined by shaking into chloroform, after the addition of sufficient sodium hydroxide to make the alkalinity up to N/10. Determinations of the rate of decomposition of solutions under different conditions showed that this depended very largely on the temperature. The amount of decomposition of a 10 per cent. solution (pH 9.4) in two months at 1 degree C. was less than 1 per cent.; at 20 degrees C. 1 per cent. was decomposed in three weeks, and at 39 degrees C., 22 per cent. in one month. Solutions of sodium phenylethylbarbiturate may have pH values from 8.9 to 9.9; in the first case 1 per cent. decomposition occurs in thirty days at 18.6 degrees C., in the second eighteen days is required for the same amount of decomposition.

Effect of Heating on Anaesthetic Power of Buffered Solutions of Cocaine Hydrochloride. J. Regnier and R. David. *Bull. Sci. Pharm. 40,* 650 (1933). Through *Quart. Journ. Pharm. Pharmacol. 7,* 139 (1934). When sterilized in an autoclave at 120 degrees C. for fifteen minutes, 1 per cent. solutions of cocaine hydrochloride strongly buffered with sodium carbonate-monosodium phosphate or with mono- and disodium phosphate, entirely lose their anaesthetic power if they are alkaline or neutral and the greater part of this property if they are acid. If buffered weakly with calcium or magnesium carbonate in the neighborhood of neutrality, the activity is wholly retained in the latter case and to the extent of 70 per cent. in the former. These buffered solutions, on sterilization, tend to approach pH 3.8. It is suggested that the opposition to this tendency by strong buffer action accounts for the loss of anaesthetic power.

SOLID EXTRACTS

When the Carpenter's Son from Bethlehem urged man to consider the lily, he anticipated the findings of our biologists by many a long century. Further proof of this kinship of ours to nature's chlorophyllic children might be deduced from the fact that certain hormones from animals speed the flowering of plants. For instance, the female sex hormone, taken from animal glands and purified into a white crystalline form, has been proved to speed the reproductive processes of plants, by two German biochemists, Walter Schoeller and Hans Goebel, of Berlin. It is probable that their experiments will be repeated in America and an effort made to put them to practical application.

Long ago the poet sang—

"And when Youth the dream departs
It takes something from our hearts
And it never comes again."

But it was only an old-fashioned way of referring to the shrinking of the thymus gland, which has long been known as the "gland of childhood." This most mysterious part of the body, the thymus gland, which is closest to the heart of any of the endocrine organs, has been recently fed to rats and conclusively proven to develop sexual precocity and speed up growth.

Practical applications to animals, perhaps even man, is foreseen because of this acceleration of the effects that occur as succeeding rat generations are given thymus extract injections. For instance, the future might see cattle raised in half the usual time, which should bring the favorite sizzling sirloin within the purview of even a professor's purse.

Paprika, a spice or condiment, mostly used by modern cooks to lend a bit of color to a dietary lay-out, now assumes a more important role. For it has been recently found to be a rich source of vitamin C—or ascorbic acid. And again we are stimulated to further research among plants long neglected in the scientific program.

Fifty years ago the noted Claude Bernard invited the grins and grimaces of skeptical medicos by stating that certain internal influences

in the pancreas were responsible for diabetes. He was given then what the slang-slingers today call the "merry ha-ha." He told them that the liver would take up the sugar from the food of the diabetic, change it into something called glycogen, and put it in storage to dole out as the muscles called for it. But in the diabetic this sugar would not burn. And Bernard said the pancreas had missed doing something to it, and despite the critics persisted in his doctrines. Today and insulin brings proof of his clear vision.

"One man's weed may be another man's feed."

So might we revamp an ancient aphorism. Farmers and gardeners, professional or amateur, know that there are such things as weeds, but most people would have some difficulty in defining one. The same plant may be a valued flower in one location and a despised weed in another, as are the poppies in the wheat in "Flanders Fields." But scientists like to put names and tags on things, even weeds, and so an attempt has been made to give a strictly scientific definition of weeds by a writer in a recent scientific journal. Here it is: "A weed is an independent plant whose species is persistently obnoxious on cultivation areas." Weeds, as everybody knows, are obnoxious; hence, of course, if a plant is obnoxious it is a weed.

That diabetes is a disease of civilization, occasioned, perhaps, by the introduction of common sugar into the dietary is the nonsensical idea advanced by some writers. In an old book called *"Sydenham's Processus Integri"* we find the following passage, which dispels beyond a doubt this foolish notion:

> "Some authors say it (diabetic urine) hath a honey-like sweetness, but this I never found, although when it dries upon a linen cloth, when it has been thorow dry it has great stiffness. *Galen* says it is caused by a *Hot Intemperature* but *Paracelsus* says it is caused by the dissolution of a dry salt through mixture of another acute or sharp salt."

Old Docs Galen and Paracelsus may have known what they were talking about, but they seem to be far over our heads in this day and generation. Yet they appear to have known of the existence of diabetes even in their remote days (Galen, 120-180 A. D.) and that was long before man added the juice of the sugar cane to his morning sip of coffee.

A recent bacteriological study of the relative cleanliness of paper and metallic money has shown the coins to be much the more sanitary. On the banknotes which had been some time in circulation and subjected to frequent handling, as many as 143,000 bacteria were found. The Lancet, an English medical journal, says: "Infectious diseases may be spread by paper money more frequently than by any other article in use among the people. The dirtiest piece of copper is, from the standpoint of the bacteriologist, cleaner than newly issued paper money." The coined money is harmless because its smooth surface does not accumulate bacteria and because of the specific germicidal action of the metal itself.

Comparison of Karaya Gum and Tragacanth

1. Tragacanth has greater mucilaginous properties than Karaya. It is necessary to use fully twice as much Karaya to obtain a comparative thick mucilage with Tragacanth.

2. Maximum viscosity is obtained by boiling the Tragacanth mucilage two minutes; Karaya mucilage by manufacture without the aid of heat.

3. The greater acidity of Karaya should be considered in pharmaceutical preparations as a source of incompatibility.

4. Tragacanth mucilage becomes thicker on aging; Karaya mucilage becomes thinner on aging.

Karaya possesses the following advantages over Tragacanth:

1. More readily soluble. One per cent. of Karaya can be completely dissolved in water in thirty minutes.

2. Karaya mucilage applied to the skin produces a softer effect than Tragacanth.

3. Karaya is preferable to Tragacanth when used in hair preparations.

Tragacanth produces a very stiff effect to the hair, whereas Karaya spreads better and keeps the hair in place without the conspicuous stiff "board" effect common to Tragacanth hair products.—(*J. A. Ph. A.* xxiii, 4 p. 344.)

MEDICAL AND PHARMACEUTICAL NOTES

Cod Liver Oil as Wound Dressing

Cod liver oil, best known for its ability to prevent or cure rickets in children and to hasten their slow convalescence from infectious diseases, has found a new use as a dressing for wounds. This new use for the familiar oil was discovered by the German Prof. Löhr as a result of three years of experimenting with thousands of cases at a hospital in Magdeburg.

Combined with other fats to make a semi-solid ointment, cod liver oil speeds up the healing of wounds, apparently giving just that fillip that makes all the difference between sluggish and quick recovery.

Whether or not the speedier healing is a result of the high concentration of vitamin A and D in the oil Prof. Löhr does not know, though he considers it a possibility. He says the new ointment is no panacea and should not be used indiscriminately. He uses it in selected cases, pasting onto wounds, sores and ulcers a layer so thick that the overlying dressings do not come into contact with the raw, tender surfaces of the wound, thus eliminating pain when the dressings are changed.—*Science News.*

Prevention of Rancidity by Light Exclusion

Rays of light at the blue end of the spectrum are responsible for much of the spoilage of foods commonly termed rancidity, reports Mayne R. Coe, a chemist in the United States Department of Agriculture. He arrived at this decision while following up investigations started three years ago on the causes of rancidity in foods. He showed that chlorophyll green wrappers retard the development of this kind of spoilage almost as well as does the total exclusion of light.

The original tests were made with the object of finding some kind of container or wrapper that would greatly retard or entirely prevent the development of rancidity in oil-bearing foods. When chlorophyll green and black showed their superiority the next step was to learn how the various light rays behaved in this respect.

Black wrappers exclude all light, but black is not desirable for commercial use, so the department has recommended chlorophyll green, which gives almost as good results. The green used by Coe excluded light rays from both ends of the spectrum, so the identity of the harmful rays remained unknown.

One of the principal tests for rancidity is the development of peroxides in foods indicating the extent to which oxidation has taken place.* Using this standard of measurement, a series of tests just completed reveals that light rays in the blue end of the visible spectrum are the most active in causing rancidity. Following is a list of the colors used, in the order of their desirability for protecting foods: black, chlorophyll green, medium red, orange red, red, dark yellow, tinted yellow, blue. At the end of the test, however, rancidity had developed with all wrappers except the chlorophyll green and black.

In the recent tests aluminum foil, which had been used in comparisons with the various colored wrappers, was also found efficient in protecting both animal and vegetable oils and fats from rancidity. This is natural, as this material excludes all light. Tin foil gave equally good results but is more expensive. Where visibility is not necessary in a wrapper, foil seems to meet all the requirements. When properly sealed it excludes moisture as well as light, and retards temperature changes. An additional feature of foil is that it reflects most of the light that falls on it and thus to that extent protects the product from heat as well as moisture both of which are contributive factors in spoilage.

New and Non-Official Remedies †

The following additional articles have been accepted as conforming to the rules of the Council on Pharmacy and Chemistry of the American Medical Association for admission to New and Nonofficial Remedies. A copy of the rules on which the Council bases its action will be sent on application.

*This oxidation goes on in the dark as well as in the light, but the character of the oxidation is different. The oil which is exposed to light becomes rancid when the peroxide formation reaches a certain value; the protected oil, on the other hand, may develop an even greater peroxide value and still show no signs of ordinary rancidity. When the protected oils are subsequently exposed to light, they, too, become rancid.

† *J. A. M. A.* 102, 24, June 16, 1934, p. 2024.

NEO-SYNEPHRIN HYDROCHLORIDE.—laevo-α-hydroxy-β-methylamino-3-hydroxy ethylbenzene hydrochloride.—The hydrochloride of the laevo isomer of a synthetically prepared derivative of phenylethylamine having the formula $C_6H_4OH.CHOHCH_2NHCH_3HCl$. Neo-synephrin hydrochloride differs from synephrin tartrate in that (1) neo-synephrin hydrochloride is a salt of hydrochloric acid—synephrin tartrate is a salt of tartaric acid; (2) neo-synephrin hydrochloride is a *laevo* compound—synephrin tartrate is a *dextro* compound; and (3) the hydroxyl of the nucleus in neo-synephrin hydrochloride is in the *meta* position—in synephrin tartrate it is in the *para* position.

Actions and Uses.—Neo-synephrin hydrochloride is a vasoconstrictor which is active when administered orally. It is more powerful in vasoconstrictive ability than synephrin tartrate, and possesses a relatively low toxicity. Applied to mucous membranes it causes contraction of the small blood vessels, thus reducing swelling and congestion of such membranes. Neo-synephrin hydrochloride may be useful in the symptomatic treatment of the nasal congestion accompanying disorders of the upper respiratory tract such as sinusitis, vasomotor rhinitis and hay fever. It may also be employed in combination with a local anesthetic, for surgical or dental use.

Dosage.—For topical application to the nasal mucous membrane the 0.25 per cent. solution is ordinarily used. The 1 per cent. solution, diluted with an equal volume of physiologic solution of sodium chloride or Ringer's solution, may be used when a stronger preparation is desired. For surgical and dental anesthesia, it may be diluted in the proportion of three to four drops of the 1 per cent. solution to 10 cc. of a 2 per cent. procaine hydrochloride solution. Neo-synephrin hydrochloride is relatively stable in alkaline solutions; it may be sterilized by boiling.

Manufactured by Frederick Stearns & Company, Detroit, U. S. patent 1,680,055 (Aug. 7, 1928; expires 1945). U. S. trademark 90,142.

Solution Neo-Synephrin Hydrochloride, 0.25 Per Cent.: Neo-synephrin hydrochloride 0.25 per cent., sodium benzoate 0.1 per cent., and sodium chloride 0.8 per cent., in distilled water.

Solution Neo-Synephrin Hydrochloride, 1 Per Cent.: Neo-synephrin hydrochloride 1 per cent., sodium benzoate 0.1 per cent., and sodium chloride 0.8 per cent. in distilled water.

Neo-synephrin hydrochloride occurs as white, odorless, non-hygroscopic crystals possessing a bitter taste. It is readily soluble in water and alcohol. The aqueous solution is neutral to litmus paper. It melts between 139-141 C. The specific rotation [α] 25/D ranges between —46.2 and —47.2.

DILAUDID.—*Di*hydro-morphinone hydrochloride.—$C_{17}H_1O_3N$.-HCl. Dilaudid differs essentially from morphine hydrochloride in that one of the hydroxyl groups of the latter has been replaced by a ketone group.

Actions and Uses.—Dilaudid is closely allied both chemically and pharmacologically to morphine, having the analgesic property of morphine as well as its action on the respiratory system. Its action on the intestine is probably less marked than is that of morphine. It is more toxic than morphine and is clinically effective in doses which are considerably smaller than are necessary with that alkaloid. It has been shown experimentally and clinically that dilaudid is powerfully analgesic and that, like morphine, it can depress the respiratory mechanism profoundly. At the same time, the experimentally established ratio between effective doses of morphine and dilaudid for the protection of desirable effects is not materially different from the ratio between their toxic doses. Clinical trial has not shown that dilaudid is free from tolerance and addiction evoking properties, and, while side actions such as nausea, vomiting and constipation seem to occur less frequently than with morphine, the prolonged administration of dilaudid should be undertaken with as much caution as would be exercised with morphine itself. Dilaudid comes within the scope of the federal narcotic regulations.

Dosage.—As a sedative and for the relief of pain, the usual oral dose is 2.5 mg. (1/24 grain); in mild pain or cough, 1.3 mg. (1/48 grain) may be given orally. The customary hypodermic does is 2 mg. (1/32 grain). Clinically the dose of dilaudid necessary to produce analgesia is about one-fifth that of morphine.

Manufactured by E. Bilhuber, Inc., Jersey City, N. J. (Bilhuber-Knoll Corporation, Jersey City, N. J., distributor). No U. S. patent. German patent 380,919 (1923). U. S. trademark 298,197.

Ampules Solution Dilaudid, 2 mg. (1/32 *grain*), *1.1 cc.*: Each cubic centimeter contains dilaudid, 2 mg., in physiologic solution of sodium chloride.

Hypodermic Tablets Dilaudid, 2 mg. (1/32 *grain*).
Hypodermic Tablets Dilaudid, 3.2 mg. (1/20 *grain*).
Hypodermic Tablets Dilaudid, 4 mg. (1/16 *grain*).
Tablets Dilaudid, 2.5 mg. (1/24 *grain*).

Dilaudid occurs as a fine, white, crystalline, odorless powder; freely soluble in water, about 1 in 3; soluble in alcohol; insoluble in ether. Its aqueous solution is neutral to litmus. From aqueous solution, ammonia water and sodium hydroxide precipitate the free base, *di*hydromorphinone as fine, white crystals, soluble in an excess of sodium hydroxide.

Nitrazine Yellow—A New Indicator

Chemistry has been presented with a new chemical which is said to have advantages over litmus for indicating the difference between acid solutions and alkaline solutions at very low concentrations.

It is 2,4-dinitrobenzene-azo-1-naphthol-3,6-disulfonic acid, called nitrazine yellow for short.

Nitrazine yellow is distinctly blue in a solution of alkali such as soap or ammonia. If an acid like muriatic or vinegar is added, the solution remains blue until the alkali is neutralized. Then if a little more acid is added the solution turns gray, at an extremely low acid concentration defined by chemists as pH6.6, and beyond that point on a rising acid concentration the nitrazine yellow in the solutions turns bright yellow.

The phenyl compounds of mercury were first prepared by Otto in 1870, but it is only a few years ago (1931) that their bactericidal properties were made known by Weed and Ecker (Cleveland, Ohio), who prepared phenylmercuric nitrate and phenylmercuric chloride in pure form. Elaborate investigations by these workers show conclusively that these compounds possess a high bactericidal value and are comparatively nontoxic to animals, also that they are nonirritating, do not upset the gastric functions, and do not affect the antigenic power of vaccines.

Ortal-Sodium

Sodium *n*-hexylethyl barbiturate.—Sodium *n*-hexylethyl malonylurea.—$NaCH_3.CH_2.CH_2.CH_2.CH_2.CH_2.(C_2H_5)C\ CONHCO:NCO$

The monosodium salt of *n*-hexylethyl barbituric acid. Ortal-sodium differs from soluble barbital, U. S. P. (sodium diethylbarbiturate), in that one of the ethyl groups of the latter is replaced in the former by a *n*-hexyl group.

Actions and Uses.—The actions and uses of ortal sodium are essentially similar to those of barbital, but ortal sodium is more active than barbital and it is used in correspondingly smaller doses.

Dosage: From 0.2 to 0.4 gm. (3 to 6 grains) followed by a glass of water. It is rarely necessary to give more than 1 gm. (15 grains) in twenty-four hours. When oral administration is contraindicated, ortal sodium may be administered rectally.

Manufactured by Parke, Davis & Company, Detroit. U. S. Patent 1,624,546 (April 12, 1927; expires 1944). U. S. Trade-mark 302,616.

Capsules Ortal Sodium, 3 grains (0.2 gm.).

Caution: Aqueous solutions of ortal-sodium are not stable but decompose on standing; on boiling, a precipitation occurs with evolution of ammonia.

Ortal-sodium is an odorless, white or slightly yellowish powder, with a bitter taste; very soluble in water; soluble in alcohol; practically insoluble in ether and benzine. An aqueous solution of ortal-sodium has an alkaline reaction to litmus.